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ORIGINAL RESEARCH

ALDH2 rs671 Polymorphism Likely a Risk Factor for Hemorrhagic Stroke: A Hospital-Based Study

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Background: Hypertension is the main risk factor for hemorrhagic stroke. Aldehyde dehydrogenase 2 (ALDH2) may inhibit the occurrence of hypertension by anti-oxidative stress and vascular dilation. The purpose was to investigate the relationship of *ALDH2* polymorphisms with hemorrhagic stroke in Hakka Chinese.

Methods: A total of 329 patients with hemorrhagic stroke and 515 controls were enrolled, and medical records (smoking and drinking history, hypertension, and diabetes) were collected. The genotypes of *ALDH2* rs671 of the two groups were detected and analyzed.

Results: The proportion of the *ALDH2* rs671 G/G, G/A, and A/A genotype in patients with hemorrhagic stroke was 55.9%, 37.4%, and 6.7%, respectively, while those were 65.0%, 30.7%, and 4.3% in controls, respectively. There was statistically significant difference in *ALDH2* rs671 genotypes distribution (P=0.021) and alleles distribution (P=0.005) between patients and controls. Among hemorrhagic stroke patients, no statistically significant differences were observed between patients with *ALDH2* different genotypes. Logistic regression analysis showed that there was significantly high risk of hemorrhagic stroke in men (male vs female: adjusted OR 1.711, 95% CI 1.154–2.538, P=0.008), the presence of hypertension (with vs without hypertension: adjusted OR 16.095, 95% CI 10.958–23.641, P<0.001), and the presence of *ALDH2* rs671 G/A genotype (G/A vs G/G: adjusted OR 1.679, 95% CI 1.151–2.450, P=0.007) or A/A genotype (A/A vs G/G: adjusted OR 2.516, 95% CI 1.132–5.591, P=0.024).

Conclusion: *ALDH2* rs671 polymorphism likely a risk factor for hemorrhagic stroke.

Keywords: ALDH2, polymorphism, hemorrhagic stroke, Hakka

Introduction

Stroke is a group of diseases in which blood cannot flow into the brain due to sudden rupture or blockage of blood vessels in the brain, with high morbidity, disability, mortality and the prevalence of stroke in the young are increasing.[1] Stroke can be divided into hemorrhagic stroke and ischemic stroke.[2] Hemorrhagic stroke refers to intracranial hemorrhage and subarachnoid hemorrhage caused by intracranial aneurysm, cerebral and spinal vascular malformation, moyamoya disease and other intracranial vascular lesions under the action of blood flow. Its high mortality and disability rate seriously endanger human health.[3] Stroke is one of the leading causes of death and disability worldwide, and hemorrhagic stroke accounts for about more than 30% strokes.[4] Despite the decline in age-standardized morbidity and mortality rates since 1990, the disease burden of hemorrhagic stroke in China remains severe.[5]

Hypertension, exposure to ambient particulate pollution, smoking, and diabetes are the main risk factors for stroke burden.[4,5] In addition, the incidence of hemorrhagic stroke is believed to be the result of genetic and environmental risk factors, the role of genetic factors in the incidence of hemorrhagic stroke has been paid more and more attention. Genome-wide association study (GWAS) data has shown that aldehyde dehydrogenase 2 (*ALDH2*) gene associated with hemorrhagic stroke.[6,7] ALDH2 is a class of nicotinamide adenine dinucleotide (NAD) (P)+ dependent enzymes, which can utilize NAD (P) + as a cofactor to participate in the oxidation and metabolism of active aldehydes.[8] ALDH2 can catalyze the formation of 1.2-dinitrate and nitrite from nitroglycerin, thereby ultimately producing cyclic guanosine

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phosphate (cGMP) and NO to dilate blood vessels.[9] ALDH2 plays an anti-oxidative stress role in vivo by metabolizing 4-hydroxynonenal (4-HNE) and inhibit the occurrence of hypertension.[10] The *ALDH2* gene rs671 polymorphism (G1510A, Glu504Lys) changed the structure of ALDH2 enzyme, and the binding of coenzyme NAD (P) + to the mutant ALDH2 enzyme was impaired, and the dehydrogenation effect was weakened, leading to the decrease of the activity of ALDH2. It suggests that *ALDH2* gene polymorphisms may play an important role in hemorrhagic stroke by affecting blood pressure.

Huang et al[11] found that *ALDH2* rs671 G/G genotype is a risk factor for spontaneously deep intracerebral haemorrhage (SDICH) in the Taiwan population. The different regions, populations, lifestyles and interaction between gene polymorphisms will affect the occurrence of hemorrhagic stroke. Up to now, there has been no report on the relationship between *ALDH2* gene polymorphisms and hemorrhagic stroke in the population in mainland China. Therefore, this study aims to clarify the relationship between them in a Hakka population in southern China.

Materials and Methods

Data Collection

The data of this retrospective study including age, gender, history of smoking, history of alcohol consumption, hypertension, diabetes, were collected from the Hospital Information System (HIS) of Meizhou People's Hospital from June 2015 to June 2021. The inclusion criteria were: (1) patients diagnosed with hemorrhagic stroke; (2) patients without missing information; (3) patients aged 18 and above. The control subjects were all from the physical examination center of Meizhou People's Hospital and did not develop hemorrhagic stroke. Finally, 329 patients with hemorrhagic stroke and 565 controls were enrolled. This retrospective study was approved by the Human Ethics Committees of Meizhou People's Hospital.

Collection of Laboratory Test Data

The data of this retrospective study including *ALDH2* genotyping, and lipid levels, were collected from the Laboratory Information System (LIS) of Meizhou People's Hospital. Genomic DNA was extracted from whole blood, and *ALDH2* genotyping was performed by polymerase chain reaction (PCR)-gene chip method (BaiO Technology Co, Ltd., China). Serum samples were evaluated for lipid level indicators, such as triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B), using the Olympus AU5400 system (Olympus Corporation, Tokyo, Japan).

Statistical Analysis

Data analysis was performed using SPSS statistical software version 21.0 (IBM Inc., USA). Student's *t*-test or the Mann–Whitney *U*-test was used for continuous data analysis. Genotype composition ratios and allele frequencies of groups were analyzed by the Chi-square test. Logistic regression analysis was applied to examine the relationship between *ALDH2* rs671 different genotypes and hemorrhagic stroke. $P< 0.05$ was considered statistically significant.

Results

Characteristics of Subjects

Three hundred and twenty-nine patients with hemorrhagic stroke (214 (65.0%) men and 115 (35.0%) women) and 515 controls (362 (70.3%) men and 153 (29.7%) women) were enrolled in this study. The average age was 64.76±12.38 years and 62.15±15.85 years in hemorrhagic stroke patients and controls, respectively. There was no statistically significant difference in the proportions between hemorrhagic stroke group and controls at different ages (<60, 60–70, and >70 years old) (P=0.181). There were statistically significant differences in the percentage of subjects with a history of smoking, alcohol consumption, and hypertension (all P<0.001). The serum TC, HDL-C, LDL-C, Apo-A1, and Apo-B (all P<0.001) levels in the patients with hemorrhagic stroke were higher than that in controls (Table 1).

Table 1 Comparison of Clinical Characteristics Between Patients with Hemorrhagic Stroke and Controls

Clinical Characteristics	Total (n=844)	Controls (n=515)	Hemorrhagic Stroke (n=329)	*P* values
Age (years)				
<60, n(%)	318(37.7%)	206(40.0%)	112(34.0%)	0.181
60–70, n(%)	241(28.6%)	138(26.8%)	103(31.3%)	
>70, n(%)	285(33.8%)	171(33.2%)	114(34.7%)	
Mean age	63.17±14.64	62.15±15.85	64.76±12.38	0.011
Gender				
Male, n(%)	576(68.2%)	362(70.3%)	214(65.0%)	0.112
Female, n(%)	268(31.8%)	153(29.7%)	115(35.0%)	
History of smoking, n(%)	211(25.0%)	169(32.8%)	42(12.8%)	<0.001
History of alcohol consumption, n(%)	99(11.7%)	87(16.9%)	12(3.6%)	<0.001
Hypertension, n(%)	396(46.9%)	127(24.7%)	269(81.8%)	<0.001
Diabetes, n(%)	148(17.5%)	80(15.5%)	68(20.7%)	0.055
TG, mmol/L	1.49±1.99	1.52±2.34	1.45±1.26	0.599
TC, mmol/L	4.38±1.51	4.21±1.58	4.64±1.36	<0.001
HDL-C, mmol/L	1.23±0.46	1.18±0.47	1.30±0.45	<0.001
LDL-C, mmol/L	2.37±0.95	2.24±0.94	2.57±0.92	<0.001
Apo-A1, g/L	1.00±0.35	0.94±0.33	1.10±0.35	<0.001
Apo-B, g/L	0.75±0.28	0.72±0.26	0.81±0.29	<0.001

Frequencies of *ALDH2* rs671 Genotypes in Patients and Controls

The distribution of *ALDH2* rs671 genotype in controls (χ^2 = 0.375, *P* = 0.540) and patients with hemorrhagic stroke (χ^2 = 0.055, *P* = 0.814) was consistent with Hardy–Weinberg equilibrium, respectively. The percentage of the *ALDH2* rs671 G/G, G/A, and A/A genotype in hemorrhagic stroke patients was 55.9%, 37.4%, and 6.7%, respectively, while those were 65.0%, 30.7%, and 4.3% in controls, respectively. The frequency of G and A allele was 74.6% and 25.4% in patients with hemorrhagic stroke, respectively; G and A allele was 80.4% and 19.6% in controls, respectively. There was statistically significant difference in *ALDH2* rs671 genotype distribution (*P*=0.021) and allele distribution (*P*=0.005) between patients and controls (Table 2).

Comparison of Characteristics of Patients with Hemorrhagic Stroke Grouped by *ALDH2* rs671 Variation

Among hemorrhagic stroke patients, no statistically significant differences were observed in the percentage of history of smoking, history of alcohol consumption, and hypertension, diabetes, and the TG, TC, HDL-C, LDL-C, Apo-A1, Apo-B levels between patients with *ALDH2* rs671 different genotypes. As well, no statistically significant differences were observed in the percentage of history of smoking, history of alcohol consumption, and hypertension, diabetes, and the lipid levels between patients with G and A allele, respectively (Table 3).

Table 2 The Prevalence of *ALDH2* rs671 Variants in Cases and Controls

	Total (n, %)	Controls (n, %)	Hemorrhagic Stroke (n, %)	*P* value
Genotypes				
G/G	519(61.5%)	335(65.0%)	184(55.9%)	0.021
G/A	281(33.3%)	158(30.7%)	123(37.4%)	
A/A	44(5.2%)	22(4.3%)	22(6.7%)	
G/G + G/A	800(94.8%)	493(95.7%)	307(93.3%)	
G/A + A/A	325(38.5%)	180(35.0%)	145(44.1%)	
Alleles				
G	1319(78.1%)	828(80.4%)	491(74.6%)	0.005
A	369(21.9%)	202(19.6%)	167(25.4%)	
HWE (χ^2, *P*)	χ^2=0.546, *P*=0.460	χ^2=0.375, *P*=0.540	χ^2=0.055, *P*=0.814	

Abbreviation: HWE, Hardy-Weinberg equilibrium.

Table 3 Clinical Characteristics of Patients with Hemorrhagic Stroke Stratified by *ALDH2* rs671 Variants

Clinical Characteristics	G/G (n=184)	G/A (n=123)	A/A (n=22)	*P* values	G Allele (G/G + G/A) (n=307)	A Allele (G/A + A/A) (n=145)	*P* values
Age (years)							
<60, n(%)	70(38.0%)	34(27.6%)	8(36.4%)	0.069	104(33.9%)	42(29.0%)	0.270
60–70, n(%)	60(32.6%)	40(32.5%)	3(13.6%)		100(32.6%)	43(29.7%)	
>70, n(%)	54(29.3%)	49(39.8%)	11(50.0%)		103(33.6%)	60(41.4%)	
Mean age	63.20±12.02	66.46±12.21	68.32±14.67	0.029	64.51±12.18	66.74±12.57	0.072
Gender							
Male, n(%)	119(64.7%)	85(69.1%)	10(45.5%)	0.107	204(66.4%)	95(65.5%)	0.915
Female, n(%)	65(35.3%)	38(30.9%)	12(54.5%)		103(33.6%)	50(34.5%)	
History of smoking, n(%)	24(13.0%)	16(13.0%)	2(9.1%)	1.000	40(13.0%)	18(12.4%)	0.882
History of alcohol consumption, n(%)	9(4.9%)	3(2.4%)	0(0)	0.485	12(3.9%)	3(2.1%)	0.406
Hypertension, n(%)	154(83.7%)	99(80.5%)	16(72.7%)	0.353	253(82.4%)	115(79.3%)	0.439
Diabetes, n(%)	35(19.0%)	28(22.8%)	5(22.7%)	0.692	63(20.5%)	33(22.8%)	0.623
TG, mmol/L	1.49±1.41	1.45±1.10	1.04±0.38	0.280	1.48±1.29	1.39±1.03	0.478
TC, mmol/L	4.67±1.41	4.61±1.35	4.57±1.02	0.904	4.64±1.38	4.60±1.30	0.760
HDL-C, mmol/L	1.34±0.52	1.25±0.35	1.29±0.35	0.293	1.30±0.46	1.26±0.35	0.306
LDL-C, mmol/L	2.57±0.93	2.58±0.95	2.57±0.83	0.996	2.57±0.93	2.58±0.93	0.963
Apo-A1, g/L	1.11±0.37	1.09±0.31	1.09±0.35	0.865	1.10±0.35	1.09±0.31	0.713
Apo-B, g/L	0.82±0.29	0.81±0.31	0.78±0.21	0.831	0.81±0.30	0.80±0.29	0.737

Effect of *ALDH2* rs671 on Hemorrhagic Stroke Susceptibility

Logistic regression analysis showed that there was significantly high risk of hemorrhagic stroke in men (male vs female: adjusted OR 1.711, 95% CI 1.154–2.538, *P*=0.008), the presence of hypertension (with vs without hypertension: adjusted OR 16.095, 95% CI 10.958–23.641, *P*<0.001), and the presence of *ALDH2* rs671 G/A genotype (G/A vs G/G: adjusted OR 1.679, 95% CI 1.151–2.450, *P*=0.007) or A/A genotype (A/A vs G/G: adjusted OR 2.516, 95% CI 1.132–5.591, *P*=0.024). And there was significantly low risk of hemorrhagic stroke in the presence of history of smoking (smoking vs non-smoking: adjusted OR 0.340, 95% CI 0.203–0.569, *P*<0.001). In addition, history of alcohol consumption, and diabetes were not associated with hemorrhagic stroke after adjusting for other covariates (Table 4).

Discussion

Studies have found that the interaction of traditional risk factors, such as hypertension, diabetes, smoking, drinking, high total cholesterol, and environmental factors likely the risk factors for stroke.[12,13] In view of these possible risk factors identified, active response measures should be taken to effectively prevent stroke, but the risk of stroke was not fully clarified by these risk factors. Previous study has found that common variants in some genetic loci are associated with

Table 4 Logistic Regression Analysis of Risk Factors Associated with Hemorrhagic Stroke

Variables	Genotypes	Unadjusted Values		Adjusted Values	
		OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age (≤65/>65)		0.923(0.700–1.219)	0.574	1.412(0.991–2.012)	0.056
Gender (Male/Female)		0.787(0.586–1.056)	0.111	1.711(1.154–2.538)	0.008
History of smoking (Yes/No)		0.300(0.206–0.435)	<0.001	0.340(0.203–0.569)	<0.001
History of alcohol consumption (Yes/No)		0.186(0.100–0.346)	<0.001	0.521(0.238–1.140)	0.103
Hypertension (Yes/No)		13.697(9.709–19.324)	<0.001	16.095(10.958–23.641)	<0.001
Diabetes (Yes/No)		1.417(0.990–2.026)	0.056	0.901(0.579–1.403)	0.645
ALDH2 rs671 polymorphism					
	G/G	1.000(reference)			
	G/A	1.417(1.054–1.906)	0.021	1.679(1.151–2.450)	0.007
	A/A	1.821(0.982–3.377)	0.057	2.516(1.132–5.591)	0.024

Abbreviations: OR, odds ratio; CI, confidence interval.

stroke risk.[14] There have been a lot of studies on genetic factors in stroke risk, but relative to ischemic stroke, hemorrhagic stroke-related studies are relatively few.[15]

Several studies have reported the relationship between genetic factors and the risk of hemorrhagic stroke.[16] Such as, angiotensin converting enzyme (ACE) I/D polymorphism may increase the risk of hemorrhagic stroke.[17] Polymorphism of *ADH1B* was related to the risk of hemorrhagic stroke in a Taiwanese population.[18] Polymorphism of E-selectin gene was related to the risk of hemorrhagic stroke in an Indian population.[19] The interaction of matrix metalloproteinase-9 (MMP-9) gene polymorphisms may be related to the wind direction of hemorrhagic stroke.[20] *APOE*,[21] *RAGE, TNFRSF11B, Golgb1*,[22] *LPL*,[23] *CRP*,[24] *KCNK17*[25] polymorphisms, and some microRNAs[26] also play a role in hemorrhagic stroke. However, other studies have failed to find a link between genetic variants and hemorrhagic stroke in different populations.[27–31]

The study of *ALDH2* gene polymorphism has certain significance for the occurrence of hemorrhagic stroke. But the association between *ALDH2* gene polymorphisms and the risk of hemorrhagic stroke has been poorly studied. In a Taiwanese study, *ALDH2* rs671 was not associated with hemorrhagic stroke in alcohol drinkers.[18] In this study, *ALDH2* rs671 likely a risk factor for hemorrhagic stroke. In terms of mechanism, on one hand, chronic inflammation, tissue hypoxia and oxidative stress play crucial roles in cerebrovascular diseases.[32] ALDH2 plays a protective role against oxidative stress by metabolizing related toxic aldehydes.[33] The *ALDH2* gene rs671 polymorphism changed the structure of ALDH2 enzyme, leading to the decrease of the activity of ALDH2, and the anti-oxidative stress effect of ALDH2 was weakened. The production of reactive oxygen species (ROS) in the body exceeds the endogenous antioxidant capacity, which tilts the balance between the oxidative system and the antioxidant system toward oxidative stress, eventually leading to vascular injury.[34,35] On the other hand, hypertension is a relatively recognized risk factor for hemorrhagic stroke,[36,37] antihypertensive treatment can reduce the stroke risk.[38] ALDH2 can play an anti-oxidative stress role in vivo by metabolizing 4-HNE and inhibit the occurrence of hypertension.[10] And ALDH2 deficiency increases oxidative stress which is the predisposing factor of hypertension.[39,40] ALDH2 also can be used as nitrate reductase to catalyze the formation of 1.2-dinitrate and nitrite from nitroglycerin, thereby ultimately producing cyclic guanosine phosphate (cGMP) and NO to dilate blood vessels and inhibit the occurrence of hypertension.[9] There were some studies on the relationship between *ALDH2* polymorphisms and hypertension. *ALDH2* rs671 polymorphism was a risk factor of hypertension among males in the general population in Japan.[41] *ALDH2* rs671 A/A genotype and A allele increase the risk of hypertension, and *ALDH2* rs671 polymorphism was a risk factor of hypertension in Han Chinese.[42] *ALDH2* rs671 polymorphism may be a risk factor for hypertension in a Chinese population.[43] The interactions of *ALDH2* rs671 polymorphism and *APOE* rs429358 or rs7412 polymorphism may effect on hypertension susceptibility.[44] So, *ALDH2* rs671 polymorphism may play a role in the risk of hemorrhagic stroke by influencing susceptibility to hypertension.

Our study is the first to study on the relationship of *ALDH2* polymorphisms and hemorrhagic stroke in Chinese mainland. And the results showed that the rs671 polymorphism of *ALDH2* likely a risk factor for hemorrhagic stroke. The frequency of *ALDH2* rs671 A allele in the East Asian population is higher than that in the South Asian, American, European and African populations.[11] But it does not fully explain racial differences in the burden of stroke.[45] Therefore, the study of risk factors for hemorrhagic stroke still needs to include more people and more factors for analysis.

The study has some shortcomings. First of all, the association between this polymorphism and the grade and location of hemorrhagic stroke was not investigated in this study because some medical records of some patients were incomplete. Second, it is a study conducted among patients and examiners in a medical institution, there was inevitably selection bias as the population is not completely representative. Third, the association between common polymorphisms of *ALDH2* gene and hemorrhagic stroke were analyzed, but this study did not investigate the relationship between the full-length variation of *ALDH2* gene, gene expression level and the risk of hemorrhagic stroke. Future studies with larger sample sizes and more polymorphisms are needed to study this relationship.

Conclusion

Individuals with *ALDH2* rs671 G/A or A/A genotype have an increased risk of hemorrhagic stroke, that is to say, *ALDH2* rs671 polymorphism likely a risk factor for hemorrhagic stroke. Our study is the first to study on the relationship of

ALDH2 polymorphisms with hemorrhagic stroke in Chinese mainland, providing valuable data for the role of *ALDH2* polymorphism in diseases.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained informed consent from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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